Pharmacodynamic Parameter Estimation: Population Size Versus Number of Samples

Submitted: March 31, 2005; Accepted: April 28, 2005; Published: October 5, 2005

Suzette Girgis,^{1,2} Sudhakar M. Pai,^{1,3} Ihab G. Girgis,⁴ and Vijay K. Batra^{1,5}

¹Department of Drug Metabolism and Pharmacokinetics, Schering-Plough Research Institute, Kenilworth, NJ

²Bristol-Myers Squibb Company, Princeton, NJ 08543

³Akros Pharma Inc., Princeton, NJ 08540

⁴Princeton University, Princeton, NJ 08544

⁵Ranbaxy Laboratories Limited, Gurgaon, India

ABSTRACT

The purpose of this study was to evaluate the effects of population size, number of samples per individual, and level of interindividual variability (IIV) on the accuracy and precision of pharmacodynamic (PD) parameter estimates. Response data were simulated from concentration input data for an inhibitory sigmoid drug efficacy ($E_{\max}$) model using Nonlinear Mixed Effect Modeling, version 5 (NONMEM). Seven designs were investigated using different concentration sampling windows ranging from 0 to 3 EC_{50} (EC_{50} is the drug concentration at 50% of the $E_{\max}$) units. The response data were used to estimate the PD and variability parameters in NONMEM. The accuracy and precision of parameter estimates after 100 replications were assessed using the mean and SD of percent prediction error, respectively. Four samples per individual were sufficient to provide accurate and precise estimate of almost all of the PD and variability parameters, with 100 individuals and IIV of 30%. Reduction of sample size resulted in imprecise estimates of the variability parameters; however, the PD parameter estimates were still precise. At 45% IIV, designs with 5 samples per individual behaved better than those designs with 4 samples per individual. For a moderately variable drug with a high Hill coefficient, sampling from the 0.1 to 1, 1 to 2, 2 to 2.5, and 2.5 to 3 EC_{50} window is sufficient to estimate the parameters reliably in a PD study.

KEYWORDS: pharmacodynamics, study design, sparse sampling

INTRODUCTION

Population pharmacodynamic (PD) modeling is useful in assessing the quantitative relationships among dose, drug

response, patient covariates, and variability. The population PD approach can be used to estimate population parameters in clinical trials, and the results can be used to optimize clinical drug development. In pharmacokinetics (PK) and PD, population analysis is useful in modeling sparse data, such as those that arise from clinical trials, where few samples (typically 1 to 3) are randomly obtained from a large number (typically a few hundred) of individuals. Therefore, sparse sampling designs should be sufficiently robust to reliably capture the parameters, as well as the variability of the parameters, of the biological system under investigation.

The purpose of this work was to evaluate, by computer simulations, sparse sampling designs that would yield reliable estimates of PD parameters of a sigmoid $E_{\max}$ model. The specific objectives were as follows: (1) to identify a design that could provide unbiased and precise estimates of the PD and variability parameters, (2) to study the effect of sample size on the accuracy and precision of parameter estimates, and (3) to investigate the effect of interindividual variability (IIV) on the accuracy and precision of parameter estimates. Generalized development of sparse sampling designs, based on observational, as well as theoretical considerations, would allow its application to developmental candidates that conform to the considerations.

MATERIALS AND METHODS

PD Model

An inhibitory sigmoid $E_{\max}$ model (Equation 1) was used in the evaluations. The parameters of this model were based on theophylline-induced eosinopenia.¹ The parameter estimates are: $E_0 = 183/\mu\text{L}$, $E_{\max} = 37/\mu\text{L}$, $EC_{50} = 5.06 \text{ mg/L}$, and $\gamma = 6.22$.¹

$$E = E_0 - \left[\frac{(E_0 - E_{\max})C^\gamma}{EC_{50}^\gamma + C^\gamma} \right] \quad (1)$$

where E is the drug response, E_0 is the baseline response, $E_{\max}$ is the drug efficacy, C is the drug concentration in

Corresponding Author: Suzette Girgis, MS, PhD, Bristol-Myers Squibb Co, Route 206 and Provinceline Road, Princeton, NJ 08543; Tel: (609) 252-6053; Fax: (609) 252-6816; E-mail: suzette.girgis@bms.com

plasma, EC_{50} is the drug concentration at 50% of the E_{max} , and γ is the sigmoidicity constant.

Statistical Model

An exponential model was used to describe the IIV in all of the PD parameters as follows:

$$\theta_i = \theta_m \times (\text{EXP}(\eta_{\theta_i})) \quad (2)$$

where θ_i is the estimate for a PD parameter in the i 'th individual, θ_m represents the population mean value of this parameter, and η_{θ_i} is a normally distributed random variable with an average value of 0 and variance of ω .² The variability parameters $\omega_{EC_{50}}$, $\omega_{E_{max}}$, ω_{E_0} , and ω_{γ} were associated with the PD parameters EC_{50} , E_{max} , E_0 , and γ , respectively.

Intraindividual variability (residual error) was also described by an exponential error model as follows:

$$E_{ij} = E_{mij} \times (\text{EXP}(\varepsilon_{ij})) \quad (3)$$

where E_{ij} is the observed effect for the i 'th individual at time j , E_{mij} is the model-predicted effect for the i 'th individual at time j , and ε_{ij} is the residual error that represents the difference between the observed response and the model predicted response. ε_{ij} is a normally distributed random variable with an average value of 0 and variance of σ .²

The coefficient of variation of the IIV was initially set at 30% for all of the PD parameters. The coefficient of variation of the residual error was set at a moderate variability level of 25%.²

Simulation of Effect-Concentration Profiles

Using the PD model (Equation 1) and the theophylline parameters described above, effect-concentration profiles were simulated in nonlinear mixed effect modeling, ver-

Figure 1. Flow chart describing how the various designs were evaluated for parameter accuracy and precision.

sion 5 (NONMEM),³ taking variability into consideration. A PRED subroutine³ was used for the simulations.

Sparse Sampling Designs

As outlined in Figure 1, 7 sampling designs (Table 1), each with different sampling windows (based on EC_{50} concentration unit), were evaluated. Five designs had 4 samples per individual, whereas the other two designs had 5 samples per individual, for a total of 100 individuals per design. The designs were based on EC_{50} units rather than “raw” plasma concentrations to facilitate the extrapolation of the results of this evaluation to a general case for a drug with a large γ value. For each design, 4 or 5 random concentration points from within the appropriate sampling windows were generated for each individual in Excel (using

Table 1. Sampling Windows of the Investigated Designs

Design	Sampling Windows (EC_{50} units)*				
	(1)	(2)	(3)	(4)	(5)
1	0.1 – 0.5	0.5 – 1	1 – 1.5	1.5 – 2	NS [‡]
2	0.1 – 0.5	0.5 – 1	1 – 2	2 – 3	NS
3	0.1 – 1	1 – 1.5	1.5 – 2	2 – 3	NS
4	0.1 – 1	1 – 2	2 – 2.5	2.5 – 3	NS
5	0 [†]	0.5 – 1.5	2 – 2.5	2.5 – 3	NS
6	0.1 – 0.5	0.5 – 1	1 – 1.5	1.5 – 2	2 – 3
7	0.1 – 0.5	0.5 – 1	1 – 2	2 – 2.5	2.5 – 3

*Represents sampling intervals in terms of EC_{50} , for each design a single sample was obtained within each window.

[†]Pre-dose (baseline) measurement.

[‡]NS: not sampled.

Figure 2. Accuracy of parameter estimates using the 7 investigated designs. The horizontal line represents the 15% cutoff.

the random function). The corresponding response data were then simulated using NONMEM. For each scenario, 100 data sets were replicated. Thus, the evaluation of any particular design was based on 40,000 or 50,000 response-concentration “observations” (ie, 4 samples $\times$ 100 subjects $\times$ 100 replications or 5 samples $\times$ 100 subjects $\times$ 100 replications).

Effect of Sample Size

The effect of sample size on the accuracy and precision of parameter estimates was evaluated for designs 1, 4, and 6 with 25 and 50 “individuals.”

Effect of IIV

IIV in PD parameters was set at 30% for each of the 7 designs. Furthermore, to evaluate the effect of variability, designs 1, 4, and 6 were also assessed at a 45% level of IIV.

Parameter Estimation

For each simulated data set, PD parameters (EC_{50} , E_{max} , E_0 , and γ) and variability parameters were estimated in NONMEM using the first-order conditional estimation method (FOCE). This method requires more computer time to perform an analysis than with the first-order method (FO), especially with large data sets and/or complex structural models, and it has been found to provide more accurate and precise estimates of the variability parameters.^{3,4}

Bias and Precision of Parameter Estimates

The accuracy and precision of the estimates from each data set were evaluated using the percent prediction error (%PE) as follows:

$$\%PE = \frac{\theta_{sim} - \theta_{true}}{\theta_{true}} \times 100 \quad (4)$$

where θ_{sim} is the estimated population value of the parameter from any single simulated data set, and θ_{true} is the true population value for the parameter. The %PE was calculated for the 100 simulated data sets in each scenario. The mean and SD of %PE were used to measure the bias and precision of parameter estimates, respectively. A mean of %PE for a parameter estimate $\leq 15\%$ was accepted as being unbiased.⁵ A SD of %PE for a parameter estimate $\leq 35\%$ was accepted as being precise.⁵

RESULTS

PD Parameters

Bias and precision of parameter estimates were used to judge the performance of the designs that were evaluated. All of the designs gave unbiased estimates of all of the PD parameters (EC_{50} , E_{max} , E_0 , and γ) except for design 2 and design 5, which gave a marginally biased estimate of γ (Figure 2). All 7 of the designs gave precise estimates of all of the PD parameters (Figure 3).

Variability Parameters

All of the 7 designs gave unbiased estimates of $\omega_{EC_{50}}$, ω_{Emax} (except design 1, which gave a marginally biased estimate of ω_{Emax}), and ω_{E_0} and biased estimates of ω_{γ} (except design 2 and design 4, which gave an unbiased estimate of ω_{γ}). All of the designs gave precise estimates of $\omega_{EC_{50}}$ and ω_{E_0} and an imprecise estimate of ω_{γ} . All of the designs except designs 1, 2, and 3, gave precise estimates of ω_{Emax} . The estimate of the residual error (σ) was unbiased and precise for all of the 7 designs.

From the 7 designs initially studied, design 4, with only 4 samples per individual, was found to be a satisfactory design where a concentration up to 3 EC_{50} units can be

Figure 3. Precision of parameter estimates using the 7 investigated designs. The horizontal line represents the 35% cutoff.

Figure 4. Effect of sample size on accuracy of parameter estimates. The horizontal line represents the 15% cutoff.

achieved for a moderately variable drug (IIV = 30%). This design provides an unbiased and precise estimate of all of the PD and variability parameters with the exception of the ω_γ estimate, which was unbiased but imprecise. Design 4 could be modified to include a baseline measurement (at time 0), which then becomes design 5. This design gave estimates of PD parameters that were similar in terms of bias and precision to design 4, with the exception of γ and ω_γ estimates, which were biased with design 5. Design 1 could be used instead of design 4 in cases where a concentration of 3 EC_{50} units cannot be achieved (eg, when toxicity is encountered at high concentrations), but ω_{Emax} would be biased and imprecise. Consequently, designs 1 and 4, with 4 samples per individual, as well as design 6, with 5 samples per individual, were selected to additionally study the effect of sample size and increasing level of IIV on the accuracy and precision of parameter estimates.

Effect of Sample Size

The effect of sample size on parameter estimates was evaluated using populations of 25, 50, and 100 individuals. For

Figure 5. Effect of sample size on precision of parameter estimates. The horizontal line represents the 35% cutoff.

Figure 6. Effect of IIV on accuracy of parameter estimates. The horizontal line represents the 15% cutoff.

design 1, the reduction of sample size from 100 to 25 individuals did not affect the accuracy of parameter estimates (Figure 4); however, it affected the precision of some variability parameters (eg, ω_{EC50} and ω_{E0}) that were precise with 100 and 50 individuals but not with 25 individuals (Figure 5).

Using design 4, reducing sample size from 100 to 50 individuals did not affect the accuracy of parameter estimates, but with 25 individuals, biased estimates of ω_{EC50} and ω_{Emax} were obtained (Figure 4). Regarding the effect of sample size on precision, imprecise estimates were obtained by reducing the sample size. The reduction of sample size from 100 to 50 individuals resulted in an imprecise estimate of ω_{Emax} and ω_{E0} , and, with 25 individuals, imprecise estimate of ω_{EC50} , ω_{Emax} , and ω_{E0} were obtained (Figure 5).

For design 6 with 5 samples per individual, the accuracy of the parameter estimates were not affected by reducing the sample size from 100 to 25 individuals (Figure 4). An imprecise estimate of ω_{Emax} was obtained with 50 individuals, and imprecise estimates of ω_{EC50} , ω_{Emax} , and ω_{E0} were obtained with 25 individuals (Figure 5). Reducing the sample size to 25 individuals resulted in imprecise esti-

Figure 7. Effect of IIV on precision of parameter estimates. The horizontal line represents the 35% cutoff.

mates of all of the variability parameters but not the residual error in designs 1, 4 and 6.

Effect of IIV

Increasing IIV from 30% to 45% using design 1 did not affect the accuracy and precision of any of the parameters except γ , which was biased (Figures 6 and 7). With design 4, increasing the level of IIV resulted in biased estimates of γ , ω_{EC50} , and $\omega\gamma$. With design 6, the accuracy and precision of parameter estimates were not affected by increasing the level of IIV. Thus, design 6 was chosen to be the best design for a highly variable drug. The estimate of the residual error was still accurate and precise at the 45% level of IIV.

DISCUSSION

Simulation is a valuable tool to investigate different design issues before the execution of a clinical trial and is useful for selecting a particular design that may best meet the objective of a study. Sparse sampling designs can be useful in large populations (eg, clinical trials) in which intensive sampling is not practical.⁶ In this study, the ability of several hypothetical sparse sampling designs to provide accurate and precise estimates of PD parameters was investigated by simulating drug response data from concentration inputs using the inhibitory sigmoid E_{max} model. It is appropriate to simulate response data directly from concentration input (and not time input), because the PD model describes the concentration-effect relationship; time is not an explicit variable in the relationship. Seven designs, which differed regarding their "coverage" of the concentration-response profile, were evaluated. Design 1 had concentration samples up to 2 EC_{50} units; however, designs 2 through 7 had concentration samples up to 3 EC_{50} units. Design 1 gave imprecise and marginally biased estimates of ω_{Emax} . To estimate ω_{Emax} reliably, values at the higher end of the concentration-response range are needed. Designs 2 and 3 gave accurate but marginally imprecise estimate of ω_{Emax} , and designs 4 and 5 gave accurate and precise estimates to ω_{Emax} . This is attributable to the importance of the 2 to 3 EC_{50} sampling window in estimating the variability parameter in E_{max} . Overall, these results show that at least 2 samples are needed from the 2 to 3 EC_{50} region to get an accurate and precise estimate of ω_{Emax} . This is consistent with a similar finding by Girgis and Rosenbaum,⁷ where 3 samples per subject design were studied. It was found that at the 30% level of IIV, a design with 0.1 to 0.5, 0.5 to 1, and 1 to 3 EC_{50} units gave precise estimates of all of the PD parameters but imprecise estimate of ω_{Emax} . Sampling windows have been successfully applied in the past,⁴ and are practical from an implementation standpoint,

whereas in clinical trials it is not possible to sample individuals at fixed time points. In this simulation work, we have shown how sampling windows can be optimized for PD parameter estimation from sparse sampling. Parameter estimates obtained from the different designs were evaluated in terms of bias and precision. It has been shown that estimates of bias and precision give better descriptions of predictive performance than correlation coefficients and/or the regression of predictions with true value.⁸

For designs 1, 4, and 6, increasing the sample size from 25 to 100 individuals improved the precision of variability parameter estimates. The accuracy of variability parameter estimates was slightly affected by increasing the sample size. PD parameter estimates in terms of accuracy and precision were not affected by the sample size.

Design 6 gave accurate and precise estimates of all of the PD and variability parameters with the exception of $\omega\gamma$, at 30% and 45% levels of IIV. Thus, it was chosen to be the best design for a highly variable drug.

In general, we found that the PK/PD parameters are estimated more accurately than the variability parameters. Al-Banna et al⁹ and Ette et al¹⁰ also found that the population PK fixed-effect parameters were reliably estimated, but the IIV parameters were inaccurate for most of the sampling schemes. Sun et al⁵ and White et al² found that there was an increase in bias and an imprecision in PK parameter estimation as intersubject variability was increased.

In summary, this evaluation illustrated how parameter estimates are influenced by study design in which the underlying data are sparse. Computer simulations showed that a sparse sampling design in which concentration samples taken from the 0.1 to 1, 1 to 2, 2 to 2.5, and 2.5 to 3 EC_{50} windows performed best at moderate level of IIV (30% IIV) for a drug with a high Hill coefficient. At a higher level of IIV (45%), design 6 (0.1 to 0.5, 0.5 to 1, 1 to 1.5, 1.5 to 2, and 2 to 3 EC_{50} units) was found to perform well. Work is in progress to evaluate how similar designs can be applied to drugs with low Hill coefficients. Overall, this generalization can help PK/PD evaluations in clinical trials.

REFERENCES

1. Braat MC, Jonkers RE, Bel EH, Van Boxtel CJ. Quantification of theophylline-induced eosinopenia and hypokalaemia in healthy volunteers. *Clin Pharmacokinet*. 1992;22:231-237.
2. White DB, Walawander CA, Tung Y, Grasela TH. An evaluation of point and interval estimates in population pharmacokinetics using NONMEM analysis. *J Pharmacokinet Biopharm*. 1991;19:87-112.
3. Beal SL, Sheiner LB. *NONMEM User's Guide Parts I-VIII*, San Francisco: University of California, San Francisco, 1998.

4. Jonsson EN, Wade JR, Karlsson MO. Comparison of some practical sampling strategies for population pharmacokinetic studies. *J Pharmacokinet Biopharm.* 1996;24:245-263.
5. Sun H, Ette EI, Ludden TM. On the recording of sample times and parameter estimation from repeated measures pharmacokinetic data. *J Pharmacokinet Biopharm.* 1996;24:637-650.
6. Hashimoto Y, Sheiner LB. Designs for population pharmacodynamics: value of pharmacokinetic data and population analysis. *J Pharmacokinet Biopharm.* 1991;19:333-353.
7. Girgis S, Rosenbaum S. Optimum design for pharmacodynamics. *Clin Pharmacol Ther.* 2000;67:163.
8. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. *J Pharmacokinet Biopharm.* 1981;9:503-512.
9. al-Banna MK, Kelman AW, Whiting B. Experimental design and efficient parameter estimation in population pharmacokinetics. *J Pharmacokinet Biopharm.* 1990;18:347-360.
10. Ette EI, Howie CA, Kelman AW, Whiting B. Experimental design and efficient parameter estimation in preclinical pharmacokinetic studies. *Pharm Res.* 1995;12:729-737.